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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/559,512	12/05/2005	Yutaka Mizushima	TAK003 P330	3849

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EXAMINER	
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ART UNIT	PAPER NUMBER
1616	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/559,512	MIZUSHIMA ET AL.	
	Examiner	Art Unit	
	JAMES H. ALSTRUM ACEVEDO	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4, 6, and 13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4, 6, and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 4, 6, and 13 are pending. Applicants cancelled claims 2-3, 5, and 7-12. Applicants amended claims 1, 4, and 6. Claim 13 is new. Receipt and consideration of Applicants amended claim set and remarks/arguments submitted on November 6, 2009 are acknowledged. All rejections/objections not explicitly maintained in the instant office action have been withdrawn per Applicants' claim amendments and/or persuasive arguments. Applicants' claim amendments have necessitated new grounds of rejection set forth below (e.g. under 35 U.S.C. § 112, 2nd paragraph).

Election/Restrictions

The restriction requirement of record is maintained at this time.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4, 6, and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "the water-soluble bivalent metal compound" in line 3. There is insufficient antecedent basis for this limitation in the claim.

The remaining claims are rejected as depending from a rejected claim.

Response to Arguments

Applicant's arguments with respect to claims 1, 4, 6, and 13 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 102

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claim 1 is rejected under 35 U.S.C. 102(e) as being anticipated by Mizushima et al. (US 2006/0093670) (Mizushima-US).

The applied reference has a common inventor (i.e. Mizushima) with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Applicants claim sustained release microparticles comprising a drug other than human growth hormone and porous hydroxyapatite, wherein some of the calcium atoms of the porous hydroxyapatite microparticles have been substituted for zinc.

Mizushima-US discloses compositions comprising **porous sustained-release hydroxyapatite (i.e. an apatite derivative) microparticles comprising (i) a drug, (ii) human serum protein, (iii) a mucopolysaccharide, and zinc ions**, wherein said composition may be in a form suitable for parenteral administration (e.g. subcutaneous or intramuscular) (title; abstract; claims 1, 7, and 11). The preparation of porous sustained-release hydroxyapatite microparticles described above and comprising **zinc acetate as the source of zinc ions and BDNF (i.e. a drug) or interferon-alpha (i.e. a drug)** are exemplified in Examples 1 and 2, respectively ([0053]-[0054]). The sustained release hydroxyapatite composition contains **at least 0.01% w/w of the biologically active drug** (claim 4).

Response to Arguments

Applicant's arguments filed November 6, 2009 have been fully considered but they are not persuasive. Applicants have traversed the instant rejection by arguing that (1) the claim amendments have overcome the rejection by reciting a porous zinc-containing hydroxyapatite structure in which calcium atoms have been substituted with zinc atoms and (2) the claimed porous zinc-hydroxyapatite provide larger absorption rates of drug other than human growth hormone.

The Examiner respectfully disagrees with Applicants' arguments. Mizushima-US clearly teaches a porous hydroxyapatite structure comprising zinc in Example 2 and in claim 7, for

example. Applicants' claim 1 does not require any specific quantity of zinc substitution for calcium in the hydroxyapatite structure. Thus, a porous hydroxyapatite having a single atom of calcium displaced by zinc and having an absorbed drug reads on Applicants' claim 1. Mizushima-US' disclosed porous hydroxyapatite in Example 1 comprises absorbed interferon and contains zinc ions (i.e. at least one atom of calcium must have been displaced by the zinc ions). Therefore, Mizushima-US' disclosure properly anticipates Applicants' amended claim 1. The rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 4, 6, and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mizushima et al. (US 2006/0093670) (Mizushima-US) in view of Tomlinson et al. (U.S. Patent No. 4,157,378).

Applicant Claims

Applicants claim sustained release microparticles as described above, wherein (i) 0.1-2.0 atoms of zinc are contained in the porous hydroxyapatite relative to 10 atoms of calcium of the porous hydroxyapatite (i.e. 1-20% of the calcium is replaced with zinc) (claim 4), (ii) the water-soluble bivalent metal compound is zinc chloride (claim 6), and (iii) the amount of drug other than human growth hormone is from 2-30% w/w.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Mizushima-US are set forth above.

Tomlinson teaches a process for the substitution of divalent metal ions, **such as zinc ions** into hydroxyapatite (col. 7, lines 25-40) via **the displacement of calcium atoms is typically affect at displacement amounts of 0.1-1 cation % of calcium** (col. 7, lines 14-17). It is desirable to introduce zinc into the hydroxyapatite structure, because zinc is known to control gingival bleeding (col. 7, lines 19-20). A specific procedure to displace calcium atoms in the hydroxyapatite structure with zinc ions is set forth in Example 9 (column 16, lines 29-53) and yields a zinc-hydroxyapatite with the empirical formula of $Ca_{4.75}Zn_{0.25}(OH)(PO_4)_3$ (i.e. 5% of the

calcium has been displaced with zinc {[0.25/(4.75+0.25)] x 100 = % calcium displacement}. Tomlinson's procedure uses zinc nitrate.

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Mizushima-US lacks the express teaching of a specified amount of zinc atom displacement of calcium atoms in the hydroxyapatite structure. This deficiency is cured by the teachings of Tomlinson and conventional knowledge in the art.

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been *prima facie* obvious to a person of ordinary skill at the time of the instant invention to modify the teachings of Mizushima-US and utilize the teachings of Tomlinson to know how to control the quantity of zinc substitution for calcium within the hydroxyapatite structure, because Tomlinson teaches procedures to substitute zinc for calcium. It is noted that the concentration of zinc introduced within the hydroxyapatite (HAP) is controlled by varying the zinc concentration in the aqueous zinc solution used in Tomlinson's procedure. Thus, it is well within the skill of the ordinary artisan to adjust the quantity of zinc substituted into the HAP and the amount of zinc substitution recited in Applicants' claims overlaps with amounts typical in the art. The amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill

to determine the optimal amount of each ingredient needed to achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, the optimization of ingredient amounts would have been obvious at the time of applicant's invention. Furthermore, a prima facie case of obviousness necessarily exists when the prior art range overlaps or touches a claimed range, such as in the instant rejection. MPEP § 2144.05. Both the amount of drug taught by Mizushima-US and the amount of zinc substitution taught by Tomlinson overlap with the ranges recited in Applicants' claims and are thus prima facie obvious.

Regarding the selection of zinc chloride, it is the Examiner's position that there is no criticality in the selection of a particular water-soluble zinc salt, because the teachings of the prior art establish that water-soluble zinc salts can be used interchangeably (e.g. zinc acetate and zinc nitrate). Furthermore, an ordinary skilled artisan would be capable of selecting any known water soluble zinc salt, such as zinc chloride, to substitute zinc for calcium within the hydroxyapatite structure (see pages 33-34 of the Wikipedia Solubility Table, accessed January 14, 2010 at en.wikipedia.org/wiki/Solubility_table). Thus, it would have been prima facie obvious to select any known water-soluble zinc salt, such as zinc chloride, zinc acetate, or zinc nitrate. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Response to Arguments

Applicant's arguments with respect to claims 4, 6, and 13 have been considered but are moot in view of the new ground(s) of rejection.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 4, 6, and 13 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 7, 23, and 25 of copending Application No. 10/516,122 (copending '122). Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of sited claims claim sustained-release porous microparticles comprising an apatite derivative and each also claim embodiments wherein the microparticles comprise divalent metal ions. Independent claim

1 of the instant application has been described above. Independent claim 1 of copending '122 claims a sustained-release composition comprising porous hydroxyapatite microparticles having pores charged with a biologically active drug, a human serum protein, a mucopolysaccharide, and an embolized divalent metal ion. Claim 24 of copending '122 claims essentially the same composition of claim 1 of copending '122.

The primary difference between the cited claims is that the claims of copending '122 recite porous microparticles containing additional required components, independent claim 1 of copending '122 does not specify that the divalent metal ion is zinc, and the claims of copending '122 are drawn to a composition. The selection of zinc as the divalent metal ion for the claimed composition of copending '122 is a contemplated prima facie obvious modification of the claimed composition of copending '122, as evidenced by dependent claim 7 of copending '122, which specifies that the divalent metal ion may be zinc. Regarding the recitation in claims 4 and 6 of the instant application that the microparticles comprise a water-soluble bivalent compound (e.g. zinc chloride) this limitation represents an obvious modifications of the claims 7 and 25 of copending '122, because the only way to obtain microparticles comprising zinc ions is for these microparticles to comprise a zinc compound. This position is supported, for example, by Example 1 in the specification of copending '122, which exemplifies the preparation of porous microparticles comprising zinc ions by the addition of zinc acetate. Thus, it is reasonable to conclude that the microparticles comprising zinc ions necessarily comprise a zinc compound. The selection of a source of zinc ions, such as zinc chloride, is thus prima facie obvious. It is proper to turn to an application's disclosure as a dictionary to understand the scope of what is

meant by a term in a claim and/or to ascertain what constitutes an obvious modification. This position is supported by the courts. See *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

Regarding the amount of calcium substituted for zinc and the amount of absorbed drug, the amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient needed to achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, the optimization of ingredient amounts would have been obvious at the time of applicant's invention. Therefore, a person of ordinary skill in the art at the time of the instant invention would have found claims 1, 4, 6, and 13 *prima facie* obvious over claims 1, 7, 23, and 25of copending Application No. 10/516,122 (copending '122).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

Applicant's arguments filed November 6, 2009 have been fully considered but they are not persuasive. Applicants have traversed the instant rejection by reiterating the arguments traversing the above prior art rejections (e.g. rejection of claim 1 as being anticipated by Mizushima-US) and arguing that the claims of copending '122 do not suggest sustained-release microparticles having a porous hydroxyapatite structure wherein the microparticles (i) have

absorbed drug that is not human growth hormone and (ii) have a partial substitution of calcium atoms by zinc.

The Examiner respectfully disagrees with Applicants' traversal arguments. Regarding the reiterated traversal arguments, Applicants' claim amendments do not overcome the instant rejection, because dependent claims 7 and 25 of copending '122 claim a sustained-release composition comprising porous hydroxy-apatite microparticles embolized with a divalent metal ion selected from zinc, copper, calcium, or magnesium ion. Thus, it is a prima facie obvious modification of the claims of copending '122 to utilize zinc as the divalent metal ion. Regarding the recitation that the absorbed drug is not human growth hormone, claim 1 of copending '122 recites that the composition comprises human serum protein and a biologically active drug. Human serum protein reads on a drug that is not human growth hormone. Furthermore, looking to paragraphs [0015]-[0016] of the specification of copending '122 to ascertain the metes and bounds of the term "biologically active drug," it is clear that the biologically active drugs contemplated are dermatological drugs and sunscreens (referred to as quasi-UV drugs in paragraph [0016] of copending '122). Thus, it is clear that an obvious modification of the claims of copending '122 would be to absorb a drug other than human growth hormone, because human growth hormone is not an art-recognized sunscreen or dermatological drug. The rejection is maintained.

Conclusion

Claims 1, 4, 6, and 13 are rejected. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner is on a flexible schedule, but can normally be reached on M-F ~10am~5:30 pm, and Saturdays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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